Chapter 8

Broadening the scope of the asymmetric Heck reaction and mechanistic investigations

In this chapter, results are reported of a study to extend the scope of the Heck reaction developed in Chapter 7 with various substrates. Although all substrates gave good conversions, the enantioselectivities were lower. Analogues of the best ligand up to now were tested. It was shown that the original ligand reported in the previous chapter was most efficient; changing substituents on the amine or Taddol moiety had a deleterious effect on enantioselectivity. Furthermore, it was found that the Pd/L ratio in the active catalyst is 1/2 and the reaction mechanism probably involves a neutral pathway.

8.1 Introduction

In Chapter 7, the development of the AHR of a new dienone, catalysed by a Pd-monodentate phosphoramidite complex, was discussed. Since this is a new reaction and we do not know how broadly applicable the Pd-monodentate phosphoramidite catalysed AHR is, we decided to study analogues of the dienone in the AHR. The composition of the catalyst will also be examined, i.e. subtle changes will be made to the ligand, providing information about the structural features in the ligand that are necessary for high asymmetric induction. Furthermore, at the initiation of this work it was not known whether this enantioselective AHR proceeds through a neutral or cationic pathway. A number of experiments were performed to uncover information about this point.

8.2 Broadening the scope

In Chapter 7, only one cyclohexadienone was used as a substrate for the AHR. To study the scope of the reaction, several analogues were synthesised and examined using the optimised conditions for this reaction as determined in chapter 7 (Figure 8.1 for a general structure). The size of the acetal, the nature of the leaving group, the substituents on the aryl group and the size of the ring that is formed during the AHR were varied.

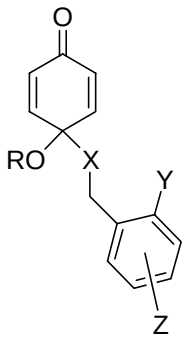
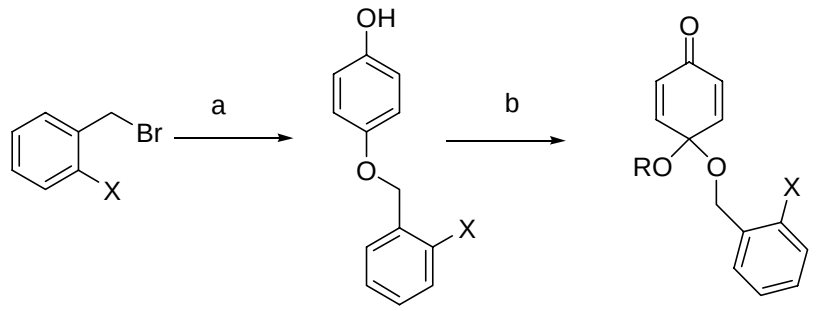


Figure 8.1 *Cyclohexadienone analogues that are substrates for the AHR*

8.2.1 Change of the leaving group

To study the effect of the leaving group a bromide-substituted analogue of dienone **8.8** was prepared. Analogously to the route reported in chapter 7 for **8.8**, 4-(2-bromo)benzyloxy-4-methoxycyclohexa-2,5-dien-2-one **8.7** was formed, starting from commercially available 2-bromobenzylbromide **8.1**, that was reacted with hydroquinone to form the mono-ether **8.4**. Phenolic oxidation using phenyliododiacetate (PIDA) yielded the dienone **8.7**. (Scheme 8.1)



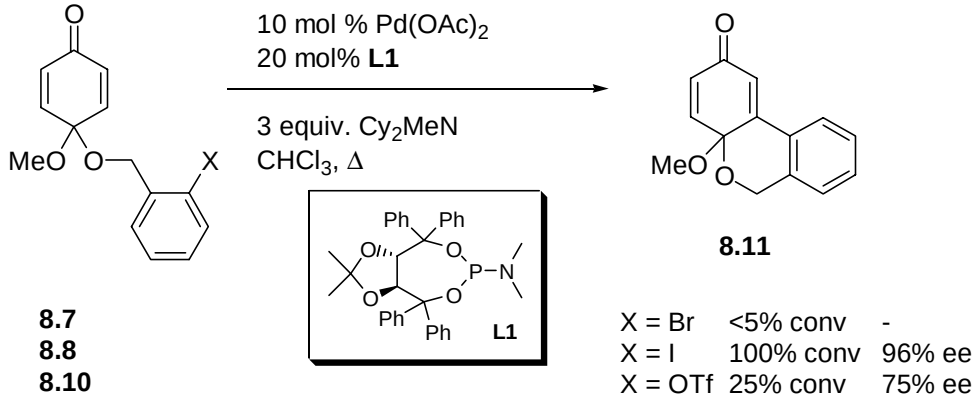
8.1 X = Br
8.2 X = I
8.3 X = OTf

8.4 X = Br
8.5 X = I
8.6 X = OTf

8.7 R = Me, X = Br
8.8 R = Me, X = I
8.9 R = *i*Pr, X = I
8.10 R = Me, X = OTf

Scheme 8.1 *Synthesis of the bromo-, iodo-, and triflate- substituted dienones. Conditions: (a) Hydroquinone, K_2CO_3, acetone, Δ. (b) PIDA, ROH.*

Starting from 2-iodobenzylbromide **8.2**, the methoxy acetal **8.8** was formed, but changing the solvent from MeOH to the more bulky *i*PrOH led to the *i*PrO- acetal **8.9** in 24 % yield.
Finally 2-(Bromomethyl)phenyl trifluoromethanesulfonate **8.3** was synthesised in 3 steps following a known method.[1] This benzyl bromide was converted to dienone **8.10** through the same monoether-oxidation sequence using PIDA as an oxidant.[2,3] The oxidation of monoether **8.6** to the dienone **8.10** was less selective, and the yield of **8.10** was only 35% after purification.



8.7
8.8
8.10

8.11

X = Br	<5% conv	-
X = I	100% conv	96% ee
X = OTf	25% conv	75% ee

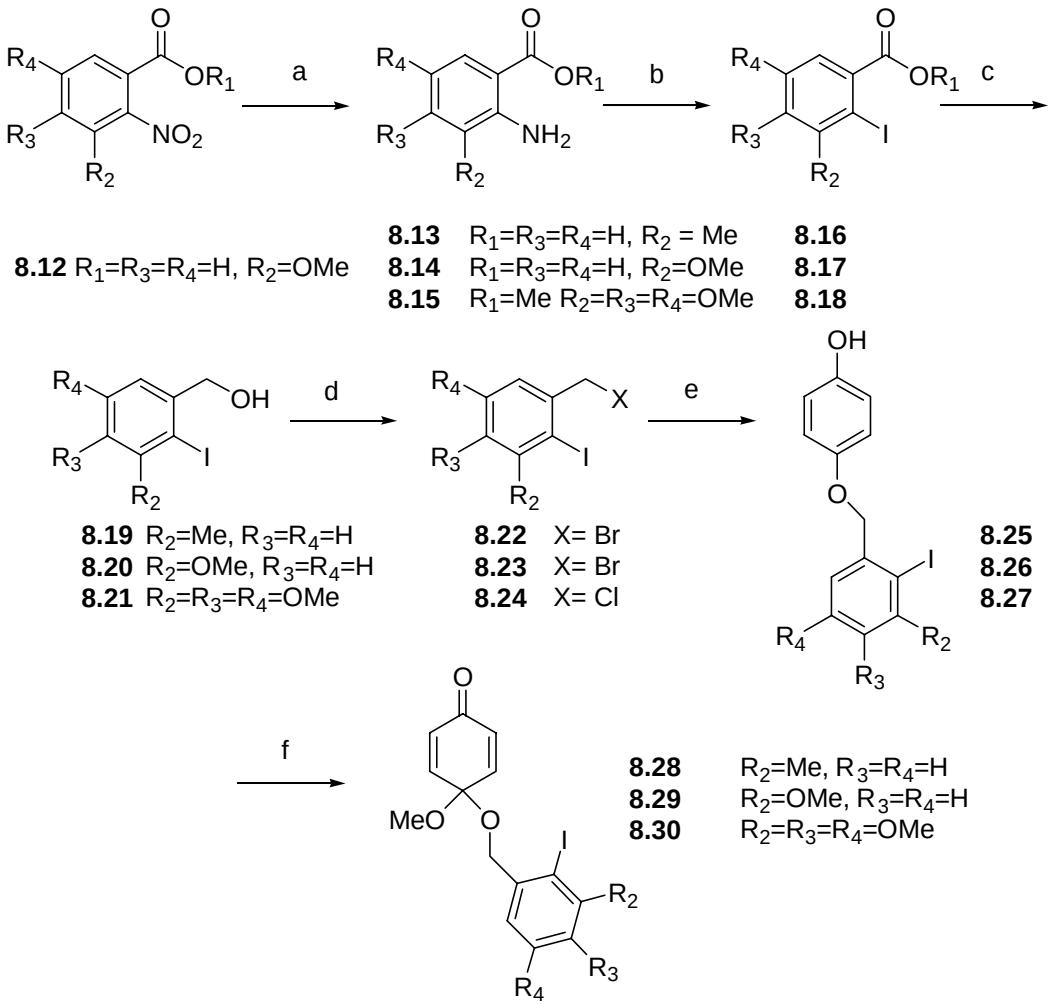
Scheme 8.2 *AHR of Br-, I-, and TfO- substituted dienones using a Pd/**L1** catalyst.*

The AHR of dienones **8.7**, and **8.10** was compared with the intramolecular coupling of iodo-dienone **8.8** described in Chapter 7. The optimised conditions for the latter substrate were employed: an *in situ* formed catalyst of $Pd(OAc)_2$ and **L1** (10 mol%, Pd/L ratio = 1/2) was utilised and the reaction was performed in $CHCl_3$, using 3 equiv. of Cy_2MeN as a base. The reaction mixture was heated to 80°C for 48 h under an inert atmosphere.

The bromo-dienone **8.7** showed only very low reactivity: less than 5% conversion was observed after a reaction time of 48h. This decrease in reactivity in Heck reactions for bromides (and chlorides) compared to iodides is well known.[4] As shown in the previous chapter, the iodo-substituted dienone **8.8** gave full conversion and the product **8.11** was isolated with an ee of 96%.
The triflate–analogue would give rise to –more of- the cationic complex (see chapter 7), which might result in a different ee and will give hints on the mechanistic pathway leading to the highest enantioselectivity (cationic or neutral).[5] The triflate **8.10** gave a very sluggish reaction: the mixture turned brown and a bit turbid. After 2 days only 25% conversion was observed (a considerable amount of side-product formation was observed as well) and the product showed only 75% ee. This indicates that in the case of these dienones, if the AHR of the triflate **8.10** would proceed mainly through a cationic pathway, and the iodide dienone **8.8** proceeds via the neutral pathway,[5] the 'neutral' complex provides the more reactive and more enantioselective pathway. (*vide infra, see section 7.2*)

8.2.2 Synthesis of dienones containing substituents on the aromatic ring

Having established that the iodides were most reactive and the AHR showed the highest enantioselectivity, we broadened the scope further by examining substituted analogues of the iodo-dienone **8.8**. Since substituted 2-iodobenzyl-halides **8.22**, **8.23** and **8.24** were not commercially available, these had to be synthesised either from 2-nitro- or 2-amino-benzoic-acids. As starting materials 3-Me-, 3-MeO- or 3,4,5-trimethoxy benzoic acids were used (see Scheme 8.3). On reduction of the commercially available nitrobenzoic acid **8.12** using Pd/C and H_2, the amine **8.14** was formed quantitatively. Treatment of the 2-amino substituted benzoic esters **8.13-8.15** with $NaNO_2$ and KI yielded the aromatic iodides **8.16-8.18** in moderate isolated yields (83%, 36% and 68%, respectively).[6] Iodobenzoic ester **8.17**, however, was not obtained as single product, but as a 68:32 mixture of **8.17** and 3-methoxybenzoic acid, the latter presumably due to reductive elimination of the iodine. We were not able to separate this mixture, and we continued the synthesis using this mixture, counting on a way to remove the reduced product in a later stage of the synthesis. Reduction of the benzoic acids **8.16** and **8.17** with $NaBH_4/I_2$[7] and reduction of 2-iodobenzoic ester **8.18** with $NaBH_4$/NaOH in EtOH provided the 2-iodobenzylalcohols **8.19-8.21** in satisfactory yields (95%, 83% and 85%, respectively). No reductive elimination of the iodine was observed. At this stage, it was possible to separate the 68:32 mixture of **8.20** and its deiodinated analogue by column chromatography. The benzylalcohols **8.19** and **8.20** were quantitatively converted to the benzylbromides using the PPh_3/CBr_4-method.[8] 2-Iodo-3,4,5-trimethoxybenzylalcohol **8.21** was converted to the corresponding benzylchloride **8.24** in 78% yield using $SOCl_2/Et_3N$.



Scheme 8.3 *Synthesis of substituted dienones. Conditions: a) Pd/C, H_2, b) $NaNO_2$, HCl, KI, c) for **8.19** and **8.20**: $NaBH_4/I_2$, THF; for **8.21**: MeOH, $NaBH_4$, NaOH, d) for **8.22** and **8.23**: CBr_4, PPh_3, CH_3CN, for **8.24**: $SOCl_2$, Et_3N, CH_2Cl_2, e) hydroquinone (10 equiv.), K_2CO_3, acetone, Δ, f) PIDA, MeOH.*

The mono-ethers **8.25-8.27** of hydroquinone were prepared in good yields (85-87%, respectively) A final PIDA oxidation in MeOH provided the dienones **8.28-8.30**, after purification by column chromatography, in 75%, 65% and 56% yield, respectively.

8.2.3 AHR of substituted dienones

For the AHR of these dienones monodentate ligand **L1** (Scheme 8.2) as well as bidentate ligand **L2** were used, employing the conditions described in the previous section. In general, all reactions proceeded with good to complete conversion (<10% of side products were formed, see chapter 7). In all cases the monodentate ligand **L1** showed higher enantioselectivity than the corresponding bidentate ligand **L2** as ee's for the products were all 2-5% lower when **L2** was employed as a ligand. The results are compiled in Table 8.1.

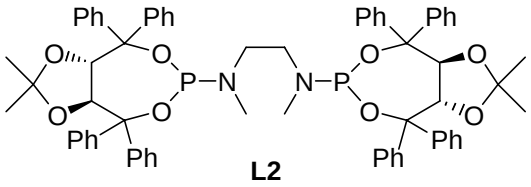


Figure 8.2 *Structure of bidentate ligand **L2***

By increasing the steric bulk around the prochiral centre (*i*PrO based acetal dienone **8.9**) a decrease in reactivity as well as enantioselectivity was observed (compare entry 1, Table 8.1 and Scheme 8.2). The product **8.31** was obtained in 89% yield and with an ee of 78% using ligand **L1**. The effect of changing the electronic and steric properties of the aryl moiety, strongly depends on the substituent pattern. For the 3-Me-substituted dienone **8.28** the ee dropped to 73% for product **8.32**. On the contrary, the presence of a 3-MeO substituent in dienone **8.29** results in product **8.33** with an ee of 94%. The presence of three MeO-groups at the aromatic ring (dienone **8.30**) results in a highly electron rich aromatic iodide and the Heck product **8.34** is obtained with 87% ee.

Table 8.1 *Results of AHR of dienones **8.8**, **8.9**, **8.28-8.30** using monodentate or bidentate phosphoramidites as chiral ligands.*[a]

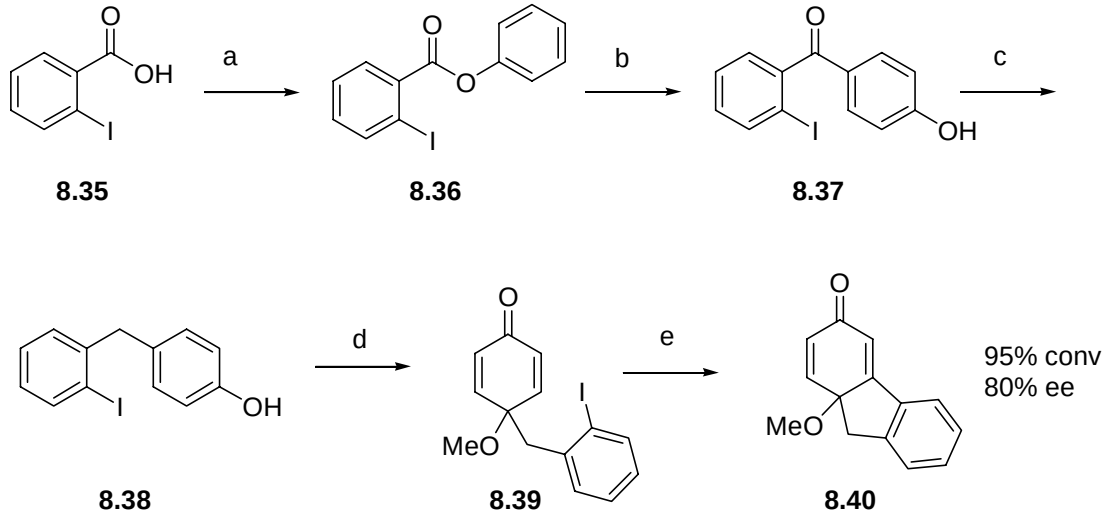
Entry	dienone	Product	Conv (%)[b] ligand **L1**	Ee (%)[c] ligand **L1**	Conv (%)[b] ligand **L2**	Ee (%)[c] ligand **L2**
1	**8.9**	**8.31**	89	78	90	73
2	**8.28**	**8.32**	95	73	98	70
3	**8.29**	**8.33**	83	94	87	92
4	**8.30**	**8.34**	84	87	80	83

[a] *Conditions: 10 mol% $Pd(OAc)_2$, 30 mol% **L1** or 20 mol% **L2**, $CHCl_3$, Cy_2MeN, Δ, 48 h;*
[b] *Determined by ^1H NMR ;* [c] *determined by chiral HPLC.*

8.2.4 Synthesis of a dienone containing a carbon-bridge.

All dienones studied sofar were dienone mono-acetals. To determine if the acetal-moiety is inextricably connected to the high ee in this intramolecular coupling reaction dienone **8.39**, which after AHR will result in an all carbon tricyclic system **8.40**, was prepared. (Scheme 8.4) This tricyclic system not only does not have an acetal moiety, but a five membered ring is formed upon Heck cyclisation is a 5-membered ring, instead of a 6-membered ring. The key step in the synthesis is the Fries-rearrangement[9] of 2-iodo-phenylbenzoic ester **8.36** to ketone **8.37** (isolated in 70%, no purification necessary). No other regioisomers were observed in this reaction. Reduction of the ketone to **8.38** using $LiAlH_4$ failed. Reduction of the ketone in the presence of the more powerful reductant $LiAlH_4/AlCl_3$[10] afforded the product **8.38** in good yield (86%). Oxididation of the phenol in the presence of PIDA/MeOH resulted in dienone **8.39**, but unfortunately this was not a very clean reaction. A number of very similar products were identified by NMR in the crude mixture, but these were difficult

to remove. Luckily, (after a few months) in one of the attempts to crystallise the product, an oil separated from the solution. This oil (only 20%) was pure dienone **8.39**. The AHR using the same conditions as for the other dienones (*vide supra*) of this new dienone resulted in 95% conversion to **8.40** (employing **L1**) and 80% ee.
Although the comparison with **8.8** is not completely justified (5 membered ring vs 6 membered ring formed), the presence of an acetal does not seem essential for high ee and good conversion.



Scheme 8.4 *Synthesis and AHR of dienone **8.39**. Conditions: a) i: $SOCl_2$, ii: NaOH, PhOH, H_2O, b) $AlCl_3$, c) $LiAlH_4/AlCl_3$ d) PIDA, MeOH, e) AHR using 10 mol% $Pd(OAc)_2$, 30 mol% **L1**, 3 equiv. Cy_2MeN, $CHCl_3$, Δ*

8.3 Additives

Added salts can enhance reactivity and selectivity in palladium mediated processes.[11,12,13] A number of experiments using bidentate ligand **L2** and the standard dienone **8.8** were performed to examine additive effects. The results are shown in Figure 8.3. As a base *i*Pr_2EtN was used with 10 mol% of Pd-cat and $CHCl_3$ was employed as the solvent. This 'standard' reaction gives full conversion after 48h and product **8.11** is obtained with 89% ee.

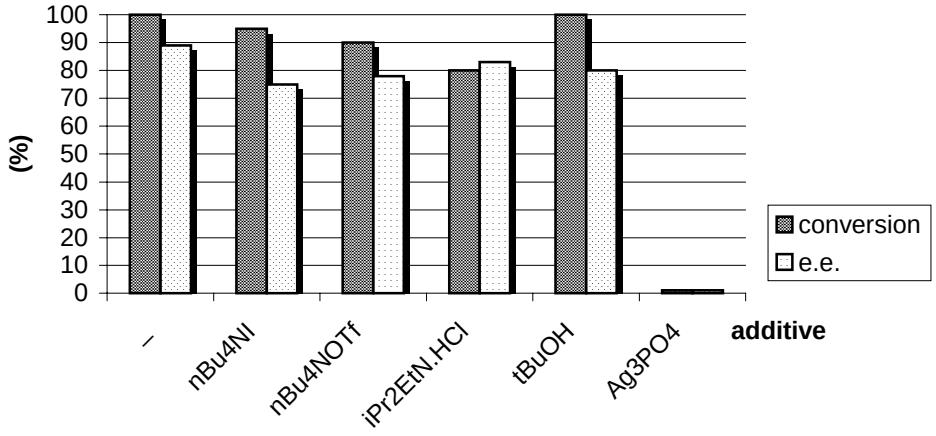


Figure 8.3 *The effect of additives on he AHR of **8.8** using the palladium catalyst based on **L2**. Conditions: 10 mol% Pd(OAc)$_2$, 20 mol% **L2**, iPr$_2$EtN, Δ, 48h. 1 equiv. of additive was used, with the exception of ^{t}BuOH, of which 10 equiv. were added.*

In the first experiment *n*Bu$_4$NI (1 equiv.) was added to the reaction mixture, to increase the I$^-$ concentration. This reaction did not go to complete conversion, and the ee of the product (75% ee) was lower than for the 'standard' reaction. Adding *n*Bu$_4$NOTf to the reaction mixture resulted in a comparable outcome: the conversion was not complete and the ee was lower. Addition of *i*Pr$_2$EtN.HCl to the mixture (mimicking the solution after a longer reaction time, since *i*Pr$_2$EtN.HI is formed as the reaction progresses)[14] resulted in a conversion of only 80%, but the ee was not affected very much. Apparently the build-up of amine salts slows down the reaction, but has little effect on ee. To our surprise, addition of *t*BuOH resulted in a clean reaction and no Pd –black was formed and full conversion was reached after 48h. This means that this reaction (with a moisture sensitive acetal) can be run in protic environment at elevated temperatures. The decrease of ee to 80% can therefore be attributed to a solvent effect. Generating the cationic complex by addition of Ag_3PO_4 or Ag_2CO_3 resulted in no conversion, which leads to the conclusion that the cationic complex is not reactive in this case. This indicates that the enantioselective AHR of **8.8**, when performed under the optimised conditions as depicted in chapter 7, will follow a neutral pathway, as the generated cationic complex is not reactive at all. The addition of salts has only a marginal effect on the enantioselectivity and conversion.

8.4 Monitoring conversion and ee in time

When we performed ^{31}P NMR on a solution of a Pd-complex formed from Pd(OAc)$_2$ and **L1** (ratio 1/3) we obtained only spectra indicating very dynamic behaviour.
To determine if the catalyst is uniformly defined throughout the reaction, the conversion and ee of the reaction was followed in time (using Cy$_2$MeN as a base and **L1** or **L2** as chiral

ligands) From the results shown in Figure 8.4 it is obvious that the ee is constant during the reaction for both ligands.

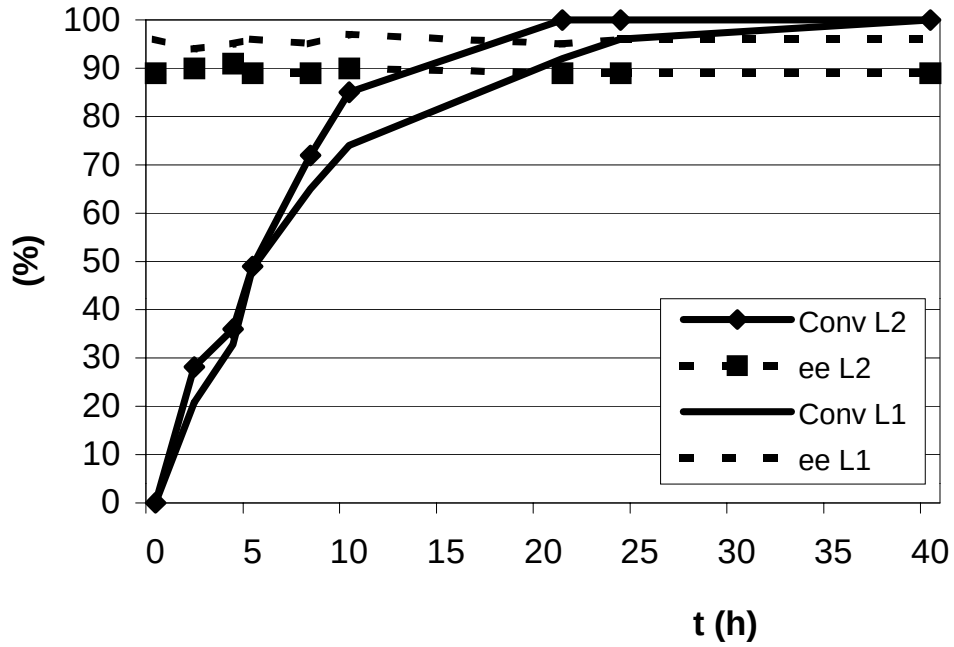


Figure 8.4 *Conversion and. ee vs. time of the AHR of **8.8** using catalysts prepared from $Pd(OAc)_2$ and **L1** or **L2**.*

From the conversion vs time plots, it is evident that they show similar behaviour; there is no induction period, which is in accordance with the constant ee observed. When 70-80 % conversion is reached, a 'levelling off' of the curve is observed, which is in accordance with the fact that the concentration of **8.8** is much lower then, giving a lower rate. This levelling off might also be due to the build-up of the $Cy_2MeN.HI$ (see also Figure 8.3)

8.5 Pd to ligand ratio

To examine if the presence of two or more equivalents of phosphoramidites is necessary for high asymmetric induction, a series of experiments was performed in which the Pd/L ratio was changed from 0-3. The ligand used for this reaction was monodentate ligand **L1** and the reactions were performed in $CHCl_3$ using Cy_2MeN as a base, whereas the catalyst was prepared using $Pd(OAc)_2$. Since this is a Pd^{II}-source, one extra equivalent of ligand was necessary for reducing the Pd^{II} to Pd^0. This extra equivalent was not included in the ratio of Pd/L.

It turned out, that even 0.5 equiv. (to Pd) of the ligand was able to induce significant ee (up to 50%) in the product. Upon increasing the ratio, also the ee of the product increased to a maximum value of 96% ee for a Pd: L ratio of 2 or higher. Increasing the amount to a Pd: L

ratio of 1:3 did not cause a further change in enantioselectivity. From this we can conclude that two equivalents of the ligand are necessary for optimal asymmetric induction, and that extra equivalents do not change the enantioselectivity of the catalyst.

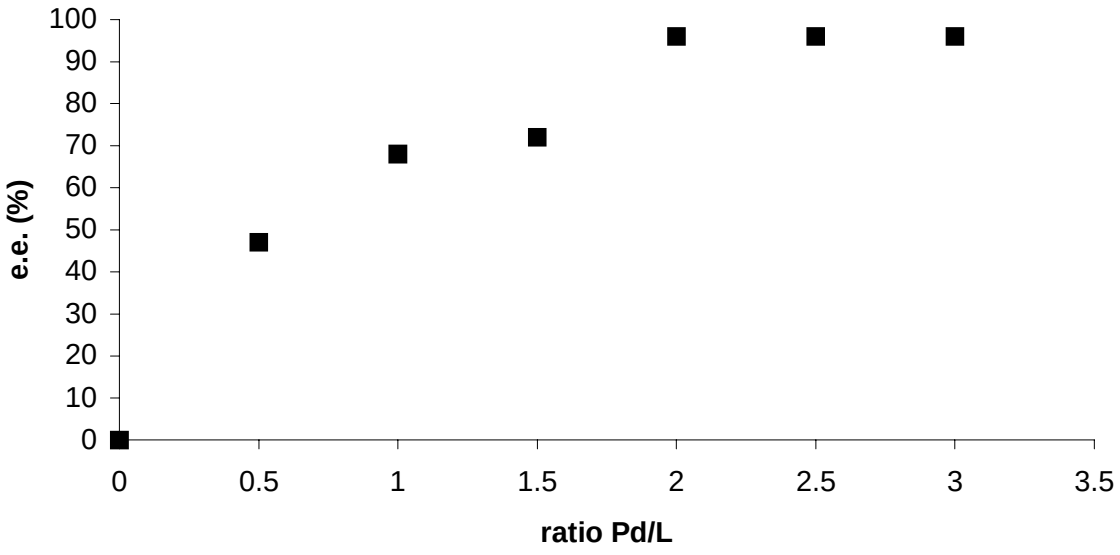


Figure 8.5 *Effect of Pd/**L-1** ratio on ee of the product at full conversion, using a catalyst prepared from $Pd(OAc)_2$ and **L1**.*

8.6 Influence of ligand structure on reactivity and selectivity

The catalyst based on phosphoramidite **L1** was superior with respect to enantioselectivity and activity to the bidentate ligand **L2**. Two equivalents of ligand are necessary for optimal asymmetric induction. To examine the steric requirements of the chiral ligand, several analogues of ligand **L1** were synthesised. The rigidity and steric effect of the amine part was subtly changed in **L3** and **L4**. The bulk of the Taddol moiety was increased in the naphthyl-analogue **L5**.[15] The cyclopentanone-acetal TADDOL derivative, that is more constrained but less hindered due to the presence of the 5-membered ring, was used to prepare the dimethylamine phosphoramidite **L6**. All ligands were prepared according to known literature procedures.[16,17]

To determine which neutral pathway (see Scheme 8.5, *vide infra*) takes place, an analogue of **L1** with a pendant (coordinating) amine functionality was designed. In this way, a bidentate ligand was formed that was in essence the monodentate ligand **L1**, but taking up two coordination places at Pd. If the catalysis would occur through the neutral pathway analogously to the one shown in Figure 7.1 where phosphine dissociation takes place, the less strongly coordinating pendant amine group would dissociate, giving a similar complex as when **L1** would be used in this pathway.

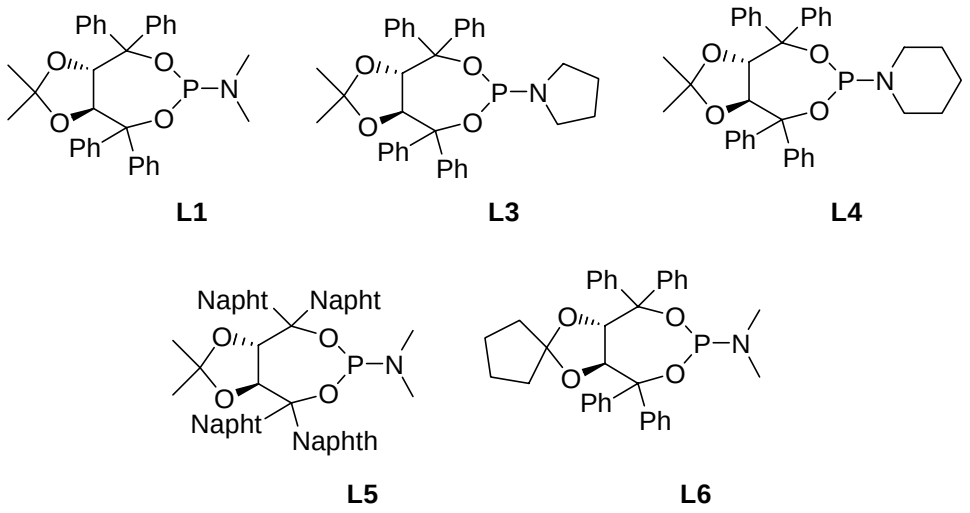


Figure 8.6 *L1 and analogues L3-L6*

The synthesis of this ligand using the addition of the N-silylamine addition to phosphorylchlorides that is common for these type of ligands,[18] was not successful, probably due to the bulk of the Taddol. The reaction of the lithiumamide of N,N',N'-trimethylethylene amine to the Taddol-derived phosphorylchloride **8.41** was more successful and ligand **L7** was obtained as a white powder, but only in low yield (13%). There was no NMR spectroscopic evidence for an intramolecular substitution at phosphorus in **L7**, giving **L7a**. This was also not observed for related phosphoramidites that have *i*PrO- groups instead of a Taddol backbone.[19]

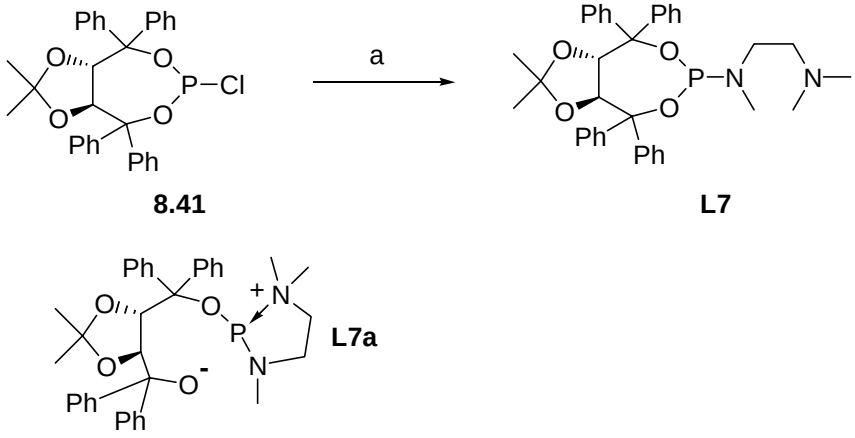
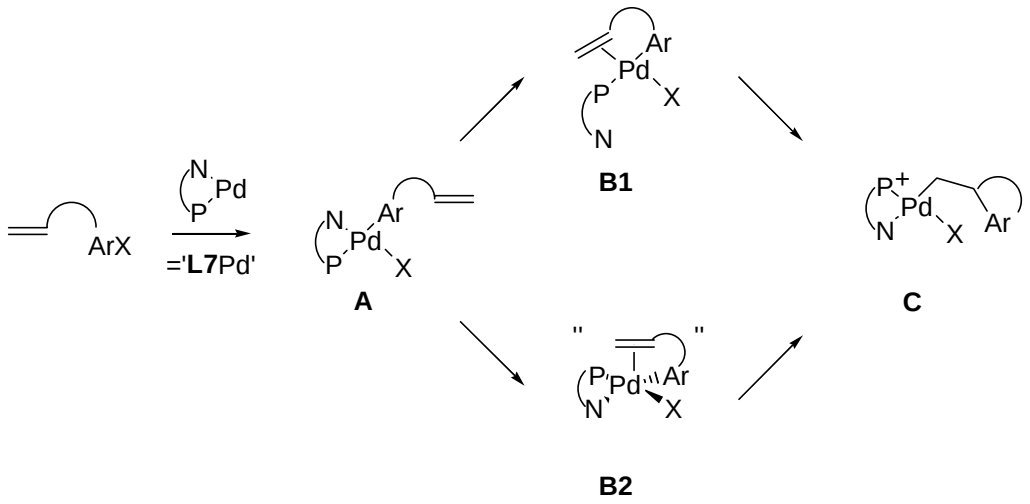


Figure 8.7 *Synthesis of bidentate **L7**. Conditions: (a) LiN(Me)CH$_2$CH$_2$N(Me)$_2$, THF.*

The AHR of substrate **8.8** was studied with these new ligands using the optimised conditions. (*vide supra*) Decreasing the bulk and the flexibility of the amine-moiety in pyrrolidine based phosphoramidite ligand **L3** provided the product with full conversion and 92% ee. By increasing the ring size as seen in **L4**, both the reactivity and selectivity decreased (to 85% conversion and 85% ee respectively). Increasing the bulk of the diol moiety in the ligand by

changing from Taddol to Dinol (naphthyl-based Taddol) resulted in **L5** that showed similar reactivity but lower enantioselectivity (full conversion, 88% ee). Changing the acetal moiety to the cyclopentanone-analogue **L6** displayed a remarkable decrease in ee to 58%, despite the remote position of modification. Excellent enantioselectivities are therefore only observed employing monodentate phosphoramidites containing small amine moieties (**L1** and **L3**), based on 'normal' Taddol.



Scheme 8.5 *Possible neutral pathways involved in the AHR of **8.8** employing **L7** as a ligand.*

Finally, the monodentate mimic **L7** resulted in a very slow reaction (only 60% conv after 48h) and a dramatic drop in ee (26% ee). The pendant dimethylamino group may coordinate too strongly to Pd in the neutral pathway, preventing dissociation to take place in path **B1** (see Scheme 8.5), resulting in path **B2**, which leads to a completely different catalyst than when **L1** is used, probably resulting in lower ee.

Figure 8.8 *Ligand variation in AHR of **8.8**.*[a]

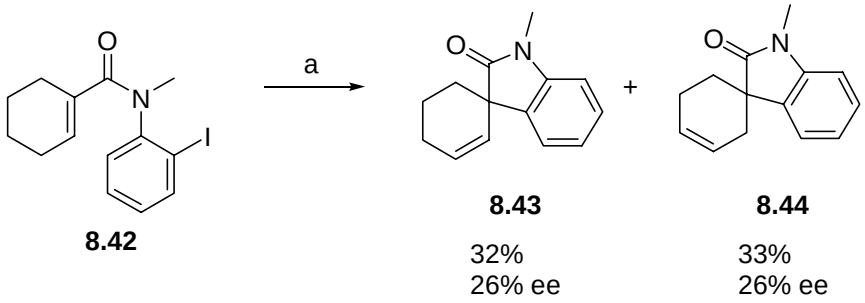
Entry	Ligand	Conv. (%)[b]	Ee (%)[c]
1	**L1**	100	96
2	**L3**	100	92
3	**L4**	85	85
4	**L5**	100	88
5	**L6**	100	58
6	**L7**	60	26

*[a] AHR of **8.8** in $CHCl_3$, using a catalyst prepared from 10 mol% $Pd(OAc)_2$ and 30 mol% ligand. Cy_2MeN was used as a base. Δ, 48h. [b] determined by ^1H NMR [c] Determined by chiral HPLC.*

However, this is unlikely, since tertiairy amines usually form dynamic complexes with Pd. A more likely explanation might be that the catalysis proceeds through the neutral five-coordinate palladium species **B2**, with a bidentate coordinating bisphosphine and axial coordination of the alkene. This again leads to the conclusion that two equiv. of phosphoramidite **L1** are necessary for high asymmetric induction

8.7 Overman substrate

Finally, to further test the phosphoramidite ligands and for comparison, the Overman substrate[20,21] was also examined. The reaction was performed under the same conditions as employed for the dienones, except for the temperature: $CHCl_3$ was used as a solvent, Cy_2MeN was used as a base and the catalyst was prepared from $Pd(OAc)_2$ and **L1**.



8.42 → **8.43** (32%, 26% ee) + **8.44** (33%, 26% ee)

Scheme 8.6 *Application of the phosphoramidite ligand in the Overman AHR. (a) 10 mol% $Pd(OAc)_2$, 20 mol% **L1**, Cy_2MeN (3 equiv.), $CHCl_3$, Δ, 18h.*

The reaction mixture was stirred overnight at ambient temperature. The conversion was only 65% and the product was formed as a 1:1 mixture of the regioisomers **8.43** and **8.44**, both having an ee of only 26%. When the reaction was performed under the conditions used by Overman (DMA, PMP) similar results were obtained.

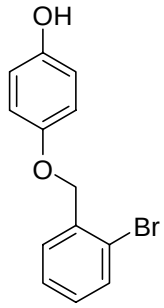
8.8 Conclusions

We have shown that the AHR of iodide substituted dienone **8.8** is very successful, resulting in full conversion and 96% ee. The cationic complex that was generated by adding silver salts to the AHR of 8.8 did not give any conversion at all. However, the triflate analogue **8.10** did show conversion albeit only 25% and an ee of 78% in the product was formed. Since the cationic complex is likely to be formed for triflates,[22] and this was shown to be unreactive, a certain percentage (25% in this case) of the amount of dienone must lead to the neutral complex resulting in a respectable enantioselectivity.
The presence of substituents at the phenyl ring results in a slower and less enantioselective Heck coupling, although an *o*-MeO-substituent is tolerated. The complex is apparently

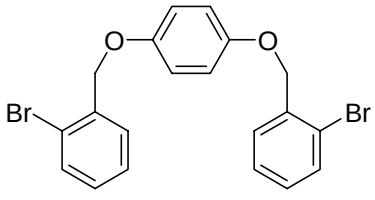
uniformly defined throughout the reaction (no induction period is necessary) and two equivalents of Taddol-based ligand **L1** are necessary for optimal asymmetric induction. Of course, this is a very interesting observation, since the bidentate version of this ligand (**L2**) shows lower enantioselectivity. Furthermore, the experiments using **L7** show that it is likely that the $Pd(OAc)_2$/**L1** catalysed AHR of **8.8** proceeds through a pentacoordinate neutral pathway.
Here, in contrast to common belief, the extra flexibility and rotational freedom that is obtained by using monodentate ligands is beneficial for the enantioselectivity of this particular Heck coupling. If this feature has generality for other AHR's still needs to be determined.
Unfortunately, until now, phosphoramidites have not been applied as ligands in other AHR or other Pd-catalysed asymmetric transformations with much success. Since these ligands are cheap, easily prepared and modified, (monodentate) phosphoramidites will certainly prove to be good ligands for various other Pd-catalysed asymmetric transformations like allylic substitutions and hydrosilylations or cascade couplings.

8.9 Experimental section

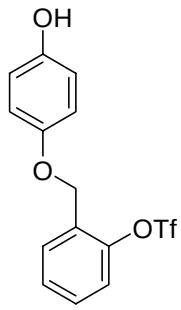
For general remarks, see previous chapters.



4-(2-Bromo)benzyloxyphenol (8.4)
(2-Bromo)-benzylbromide 5.0 g (20 mmol), 11 g (100 mmol) hydroquinone and 4.1 g (30 mmol) K_2CO_3 were dissolved in 100 ml of acetone and stirred under reflux overnight. The mixture was cooled to room temperature and the solid was removed by filtration. The remaining solution was concentrated and the residue was dissolved in $CHCl_3$. The hydroquinone precipitated and could be removed by filtration. After evaporation of the $CHCl_3$, the remaining oil was suspended in MeOH, after which the di-ether **8.4a** precipitated (0.70 g, 8%). Another filtration and solvent evaporation yielded the mono-ether as an orange oil (3.24 g, 58%).
^{1}H NMR δ 5.08 (s, 2H), 6.77 (d, *J* = 9 Hz, 2H), 6.87 (d, *J* = 9 Hz, 2H), 7.21 (m, 2H), 7.62 (m, 2H). ^{13}C NMR δ 70.15 (t), 116.07 (d), 122.27 (s), 127.53 (d), 128.89 (d), 129.154 (d), 132.56 (d), 136.49 (s), 149.86 (s), 152.61 (s). CI for $C_{13}H_{11}O_2Br$ 296.2 (100%), 298.2 (99.7%).



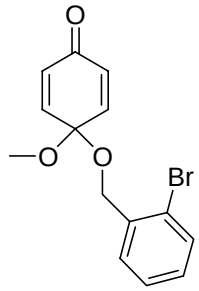
1,4-Di-(2-bromo)benzyloxybenzene (8.4a)
^{1}H NMR δ 5.09 (s, 4H), 6.93 (s, 4H), 7.31 (m, 4H), 7.59 (m, 4H). ^{13}C NMR δ (68.54 (t), 114.36 (d), 120.75 (s), 126.03 (d), 127.37 (d), 127.66 (d), 131.07 (d), 135.00 (s), 151.47 (s). HRMS calcd. for $C_{20}H_{16}O_2Br_2$ 445.951, found 445.952.



2-[(4-Hydroxyphenoxy)methyl]phenyl trifluoromethanesulfonate (8.6)

2-(Bromomethyl)phenyl trifluoromethanesulfonate **8.3**,[1] (1.0 g (3.15 mmol), 1.73 g (15.7 mmol) hydroquinone and 325 mg (3.25 mmol) Et_3N were dissolved in 10 ml of acetone and the mixture was stirred under reflux for 16h. The mixture was filtered, the filtrate concentrated and the product was purified by column chromatography (SiO_2, Hexane/EtOAc = 8/1) yielding pure **8.6** as a colorless oil (696 mg, 67%).

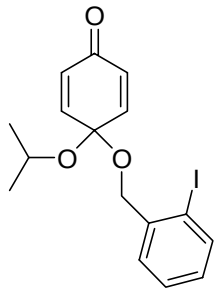
^{1}H NMR δ 5.14 (s, 2H), 6.81 (d, *J* = 9 Hz, 2H), 7.04 (d, *J* = 9 Hz, 2H), 7.32 (m, 3H), 7.58 (m, 1H). ^{13}C NMR δ 65.10 (t), 116.09 (d), 116.46 (d), 122.28 (d), 128.51 (d), 129.66 (d), 130.15 (d), 142.59 (s), 150.41 (s) 151.95 (s), 156.08 (s). HRMS calcd. for $C_{14}H_{11}O_5F_3S$ 348.028, found 348.028.



4-(2-Bromo)benzyloxy-4-methoxycyclohexa-2,5-dien-2-one (8.7)

To a stirred solution of 2.0 g (7.2 mmol) of 4-(2-bromo)benzyloxyphenol (**8.4**) in dry MeOH (10 ml) was added over 30 min a solution of 2.3 g (7.2 mmol) phenyliododiacetate in MeOH (50 ml). After 17h, the mixture was diluted with water (150 ml) and extracted with Et_2O (3x 50 ml). The combined organic layers were extracted with 2N NaOH (50 ml), brine (50 ml), dried on Na_2SO_4 and the solvent evaporated. The remaining oil was purified by column chromatography (SiO_2, Hexane/EtOAc = 8/1), yielding the product as an orange oil (1.56 g, 70%).

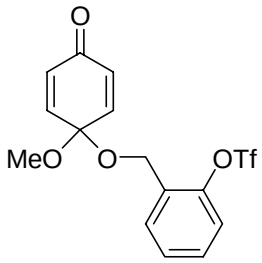
^{1}H NMR δ 3.44 (s, 3H), 4.72 (s, 2H), 6.30 (d, *J* = 7 Hz, 2H), 6.91 (d, *J* = 7Hz, 2H), 7.17 (m, 1H), 7.33 (m, 3H), 7.51 (m, 2H). ^{13}C NMR δ 49.30 (q), 62.82 (t), 92.31 (s), 120.82 (s), 126.00 (d), 127.47 (d), 127.67 (d), 128.48 (d), 131.02 (d), 135.33 (s), 141.67 (d), 183.78 (s). HRMS calcd. for $C_{14}H_{13}O_3Br$ 308.005, found 308.004.



4-(2-Iodo)benzyloxy-4-isopropoxycyclohexa-2,5-dien-2-one (8.9)

To a solution of 3.0 g (11.7 mmol) of 4-(2-iodo)benzyloxyphenol in 3 ml of CH_3CN were added 15 ml of ^{i}PrOH and a solution of 3.75 g (11.7 mmol) of PIDA in 30 ml of CH_3CN. The reaction mixture was stirred 16h. The solvents were evaporated and 200 ml of water was added. The waterlayer was extracted 3 times with 50 ml of diethylether, the combined organic layers were washed with brine, dried with Na_2SO_4 and the solvent evaporated. The crude product was purified by column chromatography (SiO_2, Hexane/EtOAc = 8/1), yielding **8.9** as an orange oil (1.1 g, 2.80 mmol, 24%).

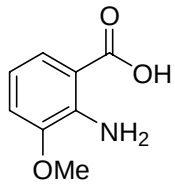
^{1}H NMR δ 1.17 (d, *J* = 6 Hz, 6H), 4.15 (septet, *J* = 6 Hz, 1H), 4.56 (s, 2H), 6.22 (d, *J* = 10 Hz, 2H), 6.92 (d, *J* = 10 Hz, 2H), 6.95 (t, *J* = 4 Hz, 1H), 7.38 (m, 2H), 7.74 (d, *J* = 9 Hz, 1H).^{13}C NMR δ 24.39 (q), 66.25 (t), 68.91 (d), 92.78 (s), 97.08 (s), 128.24 (d), 128.40 (s), 128.59 (d), 129.18 (d), 129.22 (d), 139.92 (s), 144.23 (d), 185.34 (s). HRMS calcd. for $C_{16}H_{17}IO_3$ 384.082, found 384.083.



Trifluoro-methanesulfonic acid 2-(1-methoxy-4-oxo-cyclohexa-2,5-dienyloxymethyl)-phenyl ester (8.10)

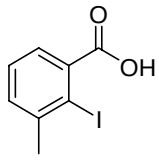
To a stirred solution of 696 mg (2.11 mmol) of **8.6** in 5 ml of MeOH, was added over a period of 15 min, a solution of 2.11 mmol (676 mg) of PIDA in 10 ml of MeOH at ambient temperature. Water (100 ml) was added and the mixture was extracted with EtOAc (3x 50 ml). The combined organic layers were washed with 1 N NaOH, brine and dried on Na_2SO_4. Filtration and concentration in vacuo yielded the crude product as a dark green oil. Purification was performed by column chromatography (SiO_2, Pet. Ether 40:60/EtOAc = 9/1) yielding the product as a pink oil (279 mg, 35%).

^{1}H NMR δ 3.30 (s, 3H), 4.72 (s, 2H), 6.19 (d, *J* = 10 Hz, 2H), 6.19 (d, *J* = 10 Hz, 2H), 7.1-7.5 (m, 3H). ^{13}C NMR δ 50.30 (q), 59.30 (t), 92.44 (s), 116.37 (d), 128.46 (s), 129.78 (d), 129.89 (d), 133.71 (d), 134.91 (d), 143.43 (d), 157.47 (s), 185.17 (s). HRMS calcd. for $C_{15}H_{13}F_3O_6S$ 378.038, found 378.038.



2-Amino-3-methoxy-benzoic acid (8.14)

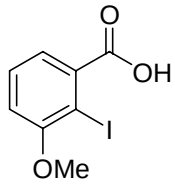
To a stirred solution of 2-nitro-3-methoxybenzoic acid (3.2 g, 16.2 mmol) (**8.12**) in ethanol was added 50 mg of Pd/C and the flask was equipped with a balloon filled with H_2. After 16 h, the mixture was filtered and the ethanol was evaporated, yielding the product as a lightly purple solid. (2.5 g, 94%). Mp 43.2-44.6 °C. (lit. 45 °C)[23] ^{1}H NMR δ 3.81 (s, 3H), 6.54 (t, *J* = 8 Hz, 1H), 6.85 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H).^{13}C NMR δ 55.72 (q), 113.50 (s), 114.661 (s), 118.34 (d), 123.19 (d), 142.45 (s), 146.98 (s), 173.54 (s). HRMS calcd. for $C_8H_9NO_3$ 167.058, found 167.056.



2-Iodo-3-methyl-benzoic acid (8.16)

A solution of 4.6 g (20.6 mmol) of **8.13** in 15 ml of conc. HCl was stirred at 0°C. After 15 min, 10 g of ice was added and a solution of 21 mmol (1.45 g) of $NaNO_2$ in 10 ml of H_2O was added slowly. After 10 min the orange solution was poured into a solution of 13.3 g (10.0 mmol) KI in 30 ml of H_2O and stirring was continued for 16 h. The mixture was extracted with diethylether (3x 100 ml) and the combined organic layers were extracted with a sat. aq. $Na_2S_2O_4$ solution (100 ml) and dried on Na_2SO_4. Evaporation of the solvent yielded the product as a yellow oil. (4.5 g, 83%).

^{1}H NMR δ 2.27 (s, 3H), 7.05 (m, 3H), 10.76 (bs, COOH), ^{13}C NMR δ 29.21 (q), 99.25 (s), 126.41 (d), 127.24 (d), 130.93 (d), 138.71 (s), 142.55 (s), 169.62 (s). HRMS calcd. for $C_8H_7O_2I$ 261.949, found 261.948.

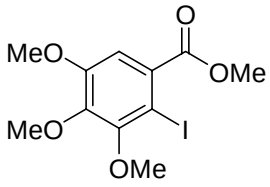


2-Iodo-3-methoxy-benzoic acid (8.17)

A solution of 3.46 g (20.7 mmol) of 2-amino-3-methoxy-benzoic acid **8.14** in 10 ml concentrated HCl was stirred at 0°C and after 15 min the solution was diluted with 10 g of ice. Slowly, a solution of 1.52 g (22 mmol) of $NaNO_2$ in

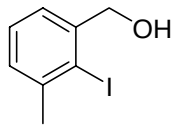
10 ml of H_2O was added. After 30 min, the bright orange solution was poured into a solution of 16 g (88 mmol) KI in 25 ml of H_20 and stirred overnight. The mixture was extracted with diethylether (3x 50 ml). The combined organic layers were extracted with aqueous $Na_2S_2O_4$, brine, dried on Na_2SO_4 and evaporated. The product (2.2 g, 36%) was isolated as a 68/32 mixture of the 2-iodo-3-methoxy benzoic acid and 3-methoxybenzoic acid and used without purification.

^{1}H NMR δ 3.77 (s, 3H), 6.78 (m, 1H), 7.18 (m, 2H), 10.6 (bs, OH) ^{13}C NMR δ 56.56 (q), 86.18 (s), 112.61 (d), 122.14 (d), 129.02 (d), 139.23 (s), 158.26 (s), 169.31 (s). HRMS calcd. for $C_8H_7O_3I$ 277.944, found 277.942.



Methyl 2-iodo-3,4,5-trimethoxybenzoate (8.18)

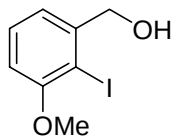
To 5.0 g (21 mmol) of methyl 2-amino-3,4,5-trimethoxy benzoate **8.15** was added 20 ml of concentrated HCl and 10 g of ice. At 0 °C, a solution of 1.6 g (23 mmol) $NaNO_2$ in 10 ml H_2O was added. After 15 min, the orange solution was added to a cooled solution of 12 g (100 mmol) KI in 30 ml H_2O and the mixture stirred overnight. The brown reaction mixture was extracted with EtOAc (3 x 30 ml), the combined organic layers were washed with aqueous $Na_2S_2O_4$, brine and dried on Na_2SO_4. Evaporation of the organic solvent yielded the product as a brown oil (3.6 g, 68%). ^{1}H NMR δ 3.80 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 2.86 (s, 3H), 7.11 (s, 1H) ^{13}C NMR δ 52.48 (q), 56.22 (q), 60.34 (q), 60.80 (q), 83.84 (s), 110.41 (d), 130.97 (s), 144.83 (s), 153.32 (s), 153.83 (s), 166.90 (s). HRMS calcd. for $C_{11}H_{13}O_5I$ 251.981, found 351.981.



2-Iodo-3-methylbenzylalcohol (8.19)

To a stirred solution of 3.6 g (13.7 mmol) of **8.16** in 100 ml of dry THF was added at 0°C 2.08 g (55 mmol) of $NaBH_4$, after which a solution of 3.5 g (13.7 mmol) I_2 in 50 ml of dry THF was added dropwise. The mixture was stirred for 16h, and was subsequently treated with 200 ml 1N HCl solution and extracted with diethylether (3 x 100 ml). The combined organic layers were washed with aqueous $Na_2S_2O_4$, brine and dried on Na_2SO_4. Evaporation of the solvent yielded the product as a cream solid. (3.1 g, 95%). Mp 70.6-71.5 °C (lit mp 70 °C).[24]

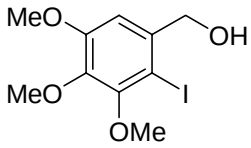
^{1}H NMR δ 2.39 (s, 3H), 3.05 (bs, OH), 4.57 (s, 2H), 7.05 (m, 3H). ^{13}C NMR δ 28.95 (q), 69.84 (t), 104.88 (s), 125.21 (d), 127.88 (d), 128.64 (d), 141.75 (s), 143.13 (s). HRMS calcd. for C_8H_9OI 247.970, found 249.973.



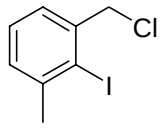
2-Iodo-3-methoxy benzyl alcohol (8.20)

To a stirred solution of 2.0 g (7.4 mmol) of a 68/32 mixture of 2-iodo-3-methoxy benzoic acid and 3-methoxy benzoic acid in 10 ml of dry THF at 0°C was added 295 mg (7.8 mmol) of $NaBH_4$ and dropwise a solution of 1.98 g (7.6 mmol) of I_2 in 25 ml of dry THF was added. The mixture was stirred overnight at ambient temperature. At 0°C, 100 ml of 1M HCl was added dropwise, and the mixture was

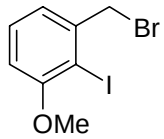
extracted with diethylether (3x 50 ml). The combined organic layers were washed with brine, dried on Na_2SO_4 and evaporated, yielding the crude products as a yellow oil. The oil was purified by column chromatography (SiO_2, Hex/Et_2O = 1/1) giving the 2-iodo-3-methoxy benzyl alcohol as a white solid (83%).
^{1}H NMR δ 3.89 (s, 3H), 4.71 (s, 2H), 6.75 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.1 Hz, 1H) ^{13}C NMR δ 56.50 (t), 69.56 (q), 89.29 (s), 110.02 (d), 120.76 (d), 129.31 (d), 144.49 (s), 157.79 (s). HRMS calcd. for $C_8H_9O_2I$ 263.965, found 263.965.



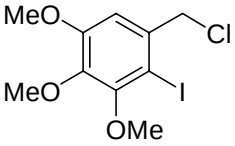
(2-Iodo-3,4,5-trimethoxyphenyl)methanol (8.21)
To a stirred solution of 2.0 g (5.6 mmol) of **8.18** and 300 mg (7.5 mmol) of NaOH in 50 ml of MeOH was added 1.2 g (32 mmol) of $NaBH_4$ and the mixture was stirred 16 h at ambient temperature. The reaction mixture was poored into 250 ml of H_2O and the aqueous layer was extracted with EtOAc (3x 50 ml). The combined organic layers were washed with brine and dried on Na_2SO_4. Evaporation of the solvent yielded the product as a yellow oil (1.54 g, 85%).
^{1}H NMR δ 3.64 (s, 3H), 3.65 (s, 3H), 3.67 (s, 3H), 4.37 (s, 2H), 4.41 (bs, OH), 6.83 (s, 1H).^{13}C NMR δ 55.70 (q), 60.36 (q), 60.56 (q), 68.15 (t), 83.20 (s), 107.09 (d), 138.89 (s), 146.61(s), 152.16 (s), 153.45 (s). HRMS calcd. for $C_{10}H_{13}O_4I$ 323.986, found 323.985.



2-Iodo-3-methylbenzylchloride (8.22)
To a stirred solution of 3.0 g (12.1 mmol) 2-iodo-3-methylbenzylalcohol **8.19** and 13.0 mmol of Et_3N (1.31 g) in 100 ml of dry CH_2Cl_2 was slowly added 12.7 mmol (1.50 g) of $SOCl_2$ at 0 °C and the resulting brown solution was stirred for 30 min. The mixture was then extracted with H_2O (2x 50 ml) and dried on Na_2SO_4. Evaporation of the solvent yielded the crude product as a brown oil, that was purified by column chromatograph (SiO_2, Hexane/ EtOAc = 8/1), to provide **8.22** (2.0 g, 62%) as an orange oil.
^{1}H NMR δ 2.44 (s, 3H), 4.70 (s, 2H), 7.20 (m, 3H). ^{13}C NMR δ 29.58 (q), 52.45 (t), 106.07 (s), 127.40 (d), 128.01 (d), 129.61 (d), 140.31 (s), 142.95 (s). HRMS calcd. for C_8H_8ClI 265.936, found 265.935.



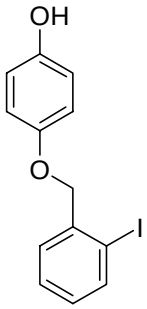
1-(Bromomethyl)-2-iodo-3-methoxybenzene (8.23)
To a stirred solution of 700 mg (2.7 mmol) 2-iodo-3-methoxy benzyl alcohol **8.20** and 1.79 g (5.4 mmol) CBr_4 in 20 ml of CH_3CN at 0°C was slowly added 1.41g (5.4 mmol) of PPh_3. The mixture was refluxed overnight, the CH_3CN was evaporated and the crude product was purified by column chromatography (SiO_2, Hexane/EtOAc = 40/1), yielding the pure **8.23** as a yellow oil (100%).
^{1}H NMR δ 3.83 (s, 3H), 4.61 (s, 2H), 6.65 (dd, *J* = 8, *J* = 1Hz, 1H), 7.08 (dd, *J* = 8, *J* = 1 Hz, 1H), 7.19 (t, *J* = 8Hz, 1H). ^{13}C NMR δ 39.39 (q), 56.61 (q), 92.54 (s), 110.54 (d), 122.77 (d), 129.47 (d), 141.87 (s) 162.91 (s). HRMS calcd. for C_8H_8BrIO 325.880, found 325.879.



1-(Chloromethyl)-2-iodo-3,4,5-trimethoxybenzene (8.24)

To a stirred solution of (2-iodo-3,4,5-trimethoxyphenyl)methanol **8.23** (1.46 g, 4.5 mmol) in 50 ml of CH_2Cl_2 was added 505 mg (5.0 mmol) triethyl amine and 531 mg (4.5 mmol) $SOCl_2$ and the mixture was stirred for 2 h at ambient temperature. The mixture was extracted with brine and dried with $NaSO_4$. Evaporation of the solvent yielded 1.2 g (78%) of the product as a yellow oil.

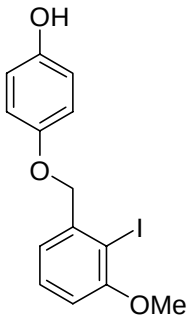
^{1}H NMR δ 3.81 (s, 6H), 3.82 (s, 3H), 4.64 (s, 2H), 6.85 (s, 1H). ^{13}C NMR δ 51.50 (t), 56.08 (q), 58.29 (q), 60.67 (q), 87.70 (s), 109.48 (d), 135.20 (s), 142.09 (s), 153.37 (s), 153.78 (s). HRMS calcd. for $C_{10}H_{12}O_3ClI$ 341.952, found 341.953.



4-[(2-Iodo-3-methylbenzyl)oxy]phenol (8.25)

To a stirred solution of 2-iodo-3-methylbenzylchloride **8.22** (2.0 g, 7.5 mmol), in 15 ml of acetone was added 1.38 g (10 mmol) of K_2CO_3 and 8.3 g (75 mmol) of hydroquinone and the mixture was stirred under reflux for 3 d. The precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The remaining brown oil was suspended in chloroform to precipitate the excess hydroquinone, which was the removed by filtration. Evaporation of the chloroform yielded the product (2.2 g, 86%) as a brown oil, which was used without purification.

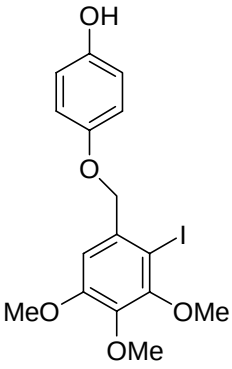
^{1}H NMR δ 2.45 (s, 3H), 4.96 (s, 2H),6.75 (d, *J* = 9 Hz, 2H), 6.81 (d, *J* = 9 Hz, 2H), 7.21 (m, 3H).^{13}C NMR δ 29.07 (q), 75.59 (t), 104.22 (s), 115.97 (d), 116.04 (d), 125.76 (d), 127.92 (d), 128.98 (d), 139.79 (s), 142.03 (s), 150,12 (s), 153.41 (s). HRMS calcd. for $C_{14}H_{13}O_2I$ 339.996, found 339.996.



4-[(2-Iodo-3-methoxybenzyl)oxy]phenol (8.26)

A stirred mixture of 1.32 g (12.0 mmol) hydroquinone, 745 mg (5.4 mmol) K_2CO_3 and 883 mg (2.7 mmol) of **8.23** in 10 ml of acetone was refluxed overnight. The mixture was filtered and the solvent evaporated. The oil was dissolved in $CHCl_3$, the solution filtered, and the filtrate concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, Hexane/EtOAc = 3/1) yielding the product as a yellow oil (819 mg, 85%).

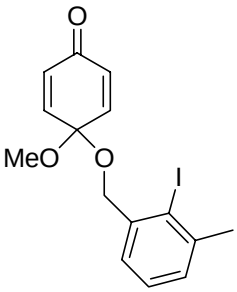
^{1}H NMR δ 3.83 (s, 3H), 4.97 (d, 2H), 6.74 (m, 3H), 6.84 (d, *J* = 7Hz, 2H), 7.10 (d, *J* = 9 Hz, 1H), 7.22 (t, *J* = 9 Hz, 1H). ^{13}C NMR δ 54.09 (q), 58.35 (t), 86.70 (s), 107.71 (d), 113.24 (d), 123.45 (d), 113.62 (d), 113.66 (d), 113.73 (d), 113.81 (d), 118.53 (d), 126.84 (d), 138.80 (s), 147.67 (s), 155.40 (s). HRMS calcd. for $C_{14}H_{13}O_3I$ 355.991, found 355.992.



4-[(2-Iodo-3,4,5-trimethoxybenzyl)oxy]phenol (8.27)

A solution of 1-(chloromethyl)-2-iodo-3,4,5-trimethoxy benzene (1.1 g, 3.2 mmol), 2.65 g (24.1 mmol) of hydroquinone and 1.07 g (7.7 mmol) of K_2CO_3 in 15 ml of acetone was stirred under reflux conditions for 16h. After cooling to room temperature, the salts were removed by filtration and the solvent evaporated in vacuo. The remaining dark oil was then suspended in 100 ml of $CHCl_3$ to precipitate the excess of hydroquinone. The hydroquinone was removed by filtration and the solvent was evaporated yielding the product as a dark oil (1.12 g, 87%).

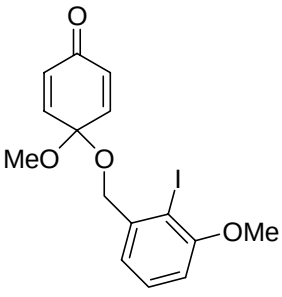
^{1}H NMR δ 3.79 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 4.90 (s, 2H), 6.63 (s, 1H), 6.72 (d, *J* = 9 Hz, 2H), 6.85 (d, *J* = 9 Hz, 2H). ^{13}C NMR δ 56.12 (q), 60.83 (q), 60.98 (q), 74.91 (t), 84.64 (s), 108.20 (d), 116.05 (d), 116.15 (d), 135.09 (s), 143.68 (s), 150.46 (s), 151.01 (s), 152.24 (s), 153.91 (s). HRMS calcd. for $C_{16}H_{17}O_5$ 416.012, found 416.013



4-[(2-Iodo-3-methylbenzyl)oxy]-4-methoxy-2,5-cyclohexadien-1-one (8.28)

To a stirred solution of 1.51 g (4.44 mmol) 4-[(2-iodo-3-methylbenzyl)oxy]phenol **8.25** in 10 ml of MeOH was added dropwise 4.5 mmol (1.45 g) of PIDA in 25 ml of MeOH at ambient temperature. The mixture was stirred overnight, diluted with 100 ml of H_2O and extracted with diethylether (3x 100 ml). The combined organic layers were dried on Na_2SO_4 and the solvent was removed by evaporation, yielding a brown oil. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc, 5/1), yielding pure **8.28** as a yellow oil. (1.2 g, 75%).

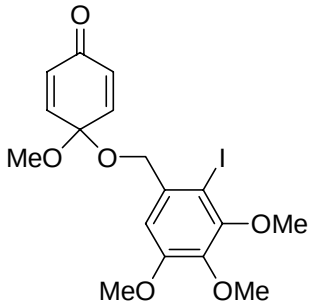
^{1}H NMR δ 2.42 (s, 3H), 3.41 (s, 3H), 4.63 (s, 2H), 6.25 (d, *J* = 10 Hz, 2H), 6.88 (d, *J* = 10 Hz, 2H), 7.18 (m, 3H).^{13}C NMR δ 27.45 (q), 49.34 (q), 68.34 (t), 91.30 (s), 103.28 (s), 124.30 (d), 126.52 (d), 127.59 (d), 128.40 (d), 138.79 (s), 140.57 (s), 141.83 (d), 183.58 (s). HRMS calcd. for $C_{15}H_{15}O_3I$ 370.007, found 370.005.



4-[(2-Iodo-3-methoxybenzyl)oxy]-4-methoxy-2,5-cyclohexadien-1-one (8.29)

To a stirred solution of 800 mg (2.53 mmol) **8.26** in 2 ml of MeOH at ambient temperature was slowly added a solution of PIDA (837 mg, 2.60 mmol) in 15 ml of MeOH. The mixture turned bright orange immediately and stirring was continued overnight. The mixture was diluted with H_2O (50 ml) and extracted with diethylether (3x 25 ml). The combined organic layers were washed with 1N KOH (20 ml), brine (20 ml) dried on Na_2SO_4 and the solvent evaporated. The crude product was purified by column chromatography (SiO_2, hexane/EtOAc = 5/1) yielding pure **8.29** as a yellow oil (65%).

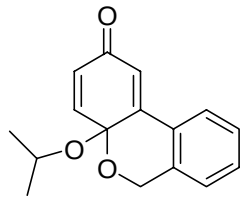
^{1}H NMR δ 3.40 (s, 3H), 3.81 (s, 3H), 4.62 (s, 2H), 6.20 (d, *J* = 11 Hz, 2H), 6.68 (d, *J* = 7Hz, 1H), 6.84 (d, *J* = 10 Hz, 2H), 6.99 (d, *J* = 7 Hz, 1H), 7.29 (t, *J* = 7 Hz, 1H) ^{13}C NMR δ 50.65 (q), 56.40 (q), 69.12 (t), 89.22 (s), 92.64 (s), 109.94 (d), 120.78 (d), 129.10 (d), 129.73 (d), 141.53 (s), 143.10 (d), 157.68 (s), 184.95 (s). HRMS calcd. for $C_{17}H_{19}IO_6$ 446.023, found 446.023.



4-[(2-Iodo-3,4,5-trimethoxybenzyl)oxy]-4-methoxy-2,5-cyclohexadien-1-one (8.30)

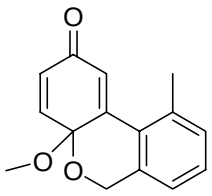
To a stirred solution of 1.0 g (2.5 mmol) of **8.27** in 10 ml of MeOH was added a solution of 837 mg (2.6 mmol) of PIDA in 10 ml of MeOH. The mixture was stirred at room temperature for 16 h and subsequently was poored into 200 ml of H_2O and extracted with diethylether (3x 100 ml). The combined organic layers were extracted with 100 ml of 1N NaOH solution and dried on Na_2SO_4. Evaporation of the solvent yielded the crude product as a brown oil. Purification by column chromatography (SiO_2, Hex: EtOAc = 8:1) yielded pure **8.30** as a yellow oil. (602 mg, 56%)
^{1}H NMR δ 3.40 (s, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.57 (s, 2H), 6.25 (d, *J* = 11 Hz, 2H), 6.80 (s, 1H), 6.86 (d, *J* = 11 Hz, 2H). ^{13}C NMR δ 50.90 (q), 60.80 (q), 60.99 (q), 69.05 (q), 74.80 (s), 92.86 (s), 108.27 (d), 130.02 (d), 135.50 (s), 141.59 (s), 143.26 (d), 152.96 (s), 153.90 (s), 185.05 (s). HRMS calcd. for $C_{17}H_{19}IO_6$ 446.023, found 446.023.

General procedure for the AHR: $Pd(OAc)_2$ **(**0.033 mmol) and 0.066 mmol of **L1** or 0.099 mmol of **L2** were dissolved under Ar in 3 ml of dry and degassed $CHCl_3$ and heated under reflux for 1-2 h, until a clear yellow solution was obtained. Next 1.2 mmol of base, the appropriate additive and 0.33 mmol of cyclohexadienone were added and the mixture was refluxed for 48 h. The solvent was evaporated, conversion was determined by ^{1}H NMR and the crude product was purified by column chromatography (SiO_2, Pet. Ether 40:60 / EtOAc = 9 /1)



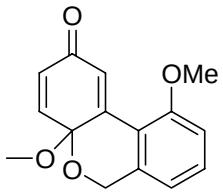
4a-isopropoxy-4aH-benzo[c]chromen-2(6H)-one (8.31)

^{1}H NMR δ 0.82 (d, *J* = 6 Hz, 3H), 1.06 (d, *J* = 8 Hz, 3H), 3.83 (septet, *J* = 6 Hz, 1H), 4.80 (d, *J* = 15 Hz, 1H), 5.11 (d, *J* = 15 Hz, 1H), 6.26 (d, *J* = 8 Hz, 1H), 6.51 (s, 1H), 6.79 (d, *J* = 14 Hz, 1H), 7.04 (d, *J* = 8 Hz, 1 H), 7.34 (m, 2H), 7.62 (d, *J* = 7Hz, 1H) ^{13}C NMR δ 23,74 (q), 24.02 (q), 62.61 (t), 66.531 (d), 119.92 (d), 123.93 (d), 124.74 (d), 127.33 (d), 128.34 (s), 129.50 (d), 130.47 (d), 135.18 (s), 144.20 (d), 14834 (s), 156.29 (s), 183.27 (s). HRMS calcd. for $C_{16}H_{16}O_3$ 256.109 found 256.107. E.e. determination on HPLC DAICEL OD column, Heptane: *i*PrOH = 95: 5, rt 12.6 min, 25.3 min.



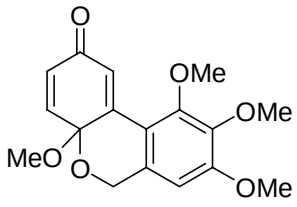
4a-Methoxy-10-methyl-4aH,6H-benzo[c]chromen-2-one (8.32)

^{1}H NMR δ 2.24 (s), 3.42 (s), 4.81 (dd, *J* = 25 Hz, 13 Hz, 2H), 6.12 (d, *J* = 11 Hz, 1H), 6.71 (s, 1H), 6.86 (d, *J* = 11Hz, 1H), 7.05-7.12 (m, 3H). ^{13}C NMR δ 17.89 (q), 42.71 (q), 63.78 (t), 114.77 (s), 121.56 (d), 126.46 (d), 129.03 (d), 130.59 (d), 131.33 (s), 131.69 (s), 135.65 (s), 142.65 (d), 149.97 (d), 164.45 (s), 198.36 (s). HRMS calcd for $C_{15}H_{14}O_3$ 242.094, found 242.093. E.e. determination on HPLC DAICEL OD column, Heptane/*i*PrOH = 95/5, rt 10.9 min, 35.94 min.



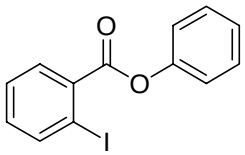
4a,10-Dimethoxy-4aH,6H-benzo[c]chromen-2-one (8.33)

^{1}H NMR δ 3.63 (s, 3H), 3.85 (s, 3H), 5.05 (d, *J* = 10Hz, 1H), 5.20 (d, *J* = 10 Hz, 1H), 6.55 (d, *J* = 8 Hz, 1H), 6.79 (s, 1H), 6.82 (d, *J* = 8 Hz, 1H), 6.87 (dd, *J* = 8 Hz, *J* = 2Hz, 1H), 7.14-7.24 (m, 1H), 7.30 (dt, *J* = 2Hz, J = 8Hz, 1H). ^{13}C NMR δ 45.4 (q), 46.3 (q), 64.1 (t), 108.1 (s), 121.3 (d), 121.4 (d), 127.3 (d), 128.2 (d), 132.1 (s), 132.4 (d), 134.6 (s), 135.3 (s), 149.8 (d), 164.5 (s), 187.0 (s). HRMS calc for $C_{15}H_{14}O_4$ 258.089, found 258.088. E.e. determination on HPLC DAICEL OD column, Heptane/*i*PrOH = 95/5, rt 18.68 min, 24.95 min.



4a,8,9,10-Tetramethoxy-4aH-benzo[c]chromen-2(6H)-one (8.34)

^{1}H NMR δ 3.24 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.98 (dd, *J* = 23 Hz, *J* = 12 Hz, 2H), 6.36 (d, *J* = 10 Hz, 1H), 6.39 (s, 1H), 6.76 (d, *J* = 9 Hz), 7.15 (d, *J* = 2 Hz). ^{13}C NMR δ 51.14 (q), 55.99 (q), 60.59 (t), 60.99 (q), 62.66 (q), 102.20 (d), 114.08 (q), 123.54 (d), 130.44 (d), 131.95 (s), 142.26 (d), 143.06 (s), 147.87 (s), 151.27 (s), 151.88 (s), 155.31 (s), 186.79 (s). HRMS calcd. for C_{17} $H_{19}O_6I$ 446.022, found 446.021. E.e. determination on HPLC DAICEL OD column, Heptane/*i*PrOH = 95/5, rt 15.9 min, 26.06 min.

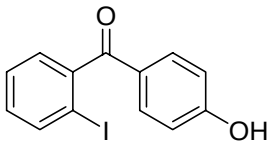


Phenyl 2-iodobenzoate (8.36)

To 10.0 g (37.5 mmol) of 2-iodobenzoic acid was added 50 ml of $SOCl_2$. The mixture was stirred for 15 min, after which the excess $SOCl_2$ was removed by distillation. The crude acid chloride **8.35** was obtained as a yellow oil and was used without purification (95% yield).

To the acid choride was added a solution of 5.7 g (mmol) of NaOH and 5.6 g (mmol) of phenol in 50 ml of water. A white oil formed instantaneously. The water layer was extracted with EtOAc (3x 50 ml) and the organic layers were dried and the solvent evaporated. The product **8.36** (11.5g, 95%) was used without purification.

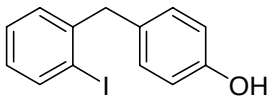
^{1}H NMR δ 7.15 (m, 4H), 7.26 (m, 3H), 8.01 (m, 2H).^{13}C NMR δ 120.45 (s), 121.54 (d), 126.09 (d), 128.03 (d), 129.49 (d), 131.44 (d), 133.18 (d), 133.35 (s),141.59 (d), 150.64 (s), 164.91 (s). HRMS calcd. for $C_{13}H_9IO_2$ 323.965, found 323.965.



(2-Iodophenyl)(4-hydroxyphenyl)methanone (8.37)

To 13.5 g (mmol) of ester **8.38** was added 8.5 g (mmol)of $AlCl_3$. The mixture was heated to 150°C for 15 min. during which the mixture changed to a dark brown, caramel-like substance. Ice-water (100 ml) was added at once. The aqueous layer was extracted with diethylether (3x 50 ml). The combined organic layers were dried with brine and Na_2SO_4. The crude mixture was purified by column chromatography (SiO_2, hexane:EtOAc, 10:1). The product was isolated as a colorless oil, which solidified upon standing. (8.8 g, 70%) mp 111.0-113.1° (lit 112°C)[25]

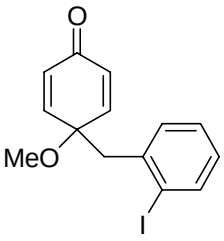
^{1}H NMR δ 6.82 (d, *J* = 9 Hz, 2H), 7.08 (t, *J* = 9 Hz,1H), 7.20 (d, *J* = 7 Hz, 1H), 7.36 (t, *J* = 8 Hz, 1H), 7.64 (d, *J* = 9 Hz, 2H), 7.83 (d, *J* = 7Hz, 1H). ^{13}C NMR δ 92.18 (d), 115.697 (s), 127.737 (d), 128.093 (s), 130.828 (d), 133.337 (d), 139.503 (d), 144.649 (s), 162.063 (s), 196.664 (s). HRMS calcd. for $C_{15}H_{11}O_2I$ 323.965 found 323.964.



4-(2-Iodobenzyl)phenol (8.38)

To a stirred solution of $LiAlH_4$ (30 ml, 1M in THF) and $AlCl_3$ (3.70 g, 30 mmol) was added 8.8 g (27.7 mmol) of **8.39**. The mixture was refluxed for 30 min, quenched with H_2O (150 ml) and extracted with diethylether (3x 100 ml). The combined organic layers were washed with brine, dried on Na_2SO_4 and the solvent evaporated, yielding the product as a colorless oil (7.4 g, 86%).

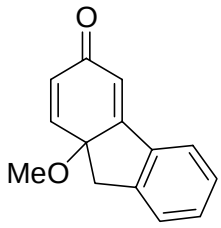
^{1}H NMR δ 3.97 (s, 2H), 5.26 (s, 1H), 6.70 (d, *J* = 8 Hz, 2H), 6.87 (t, *J* = 6 Hz, 1H), 7.01 (m, 3H), 7.18 (t, *J* = 6 Hz, 1H), 7.78 (d, *J* = 6 Hz, 1H). ^{13}C NMR δ 45.62 (t), 115.32 (d), 127.91 (d), 128.28 (d), 130.31 (d), 131.65 (s), 139.50 (s), 143.91 (s), 154.00 (s). HRMS calcd. for $C_{13}H_{11}OI$ 309.985, found 309.986.



4-(2-Iodobenzyl)-4-methoxy-2,5-cyclohexadien-1-one (8.39)

A solution of 3.9 g (12.4 mmol) of PIDA in 50 ml of MeOH was slowly added to a stirred solution of 3.8 g (12.3 mmol) of **8.40** in3 ml of MeOH. The mixture was stirred overnight, yielding a green solution with a brown sticky gum inside. The mixture was diluted with 250 ml of water and extracted with diethylether (3x 150 ml), the combined organic layers were washed with 1N aq.KOH (100 ml), brine, dried on Na_2SO_4 and the solvent evaporated. The crude mixture consisted of the desired product and an unidentified side product (2.6 g; ratio 1/1). Separation by column chromatography (SiO_2, Hexane EtOAc = 25/1) was unsuccessful. However, upon dissolving the yellow oil in a 1/1 acetone/pentane mixture and storing at 4°C for 2 months yielded a light yellow oil (832 mg, 20%) that was identified as pure **8.39**.

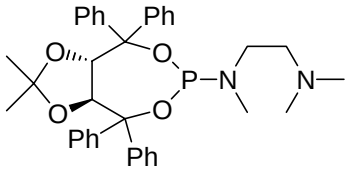
^{1}H NMR δ 3.16 (s, 3H), 3.23 (s, 3H), 6.25 (d, *J* = 10 Hz, 2H), 6.80 (d, *J* = 10 Hz, 2H), 6.85 (m, 1H), 7.18 (m, 2H), 7.76 (m, 1H).^{13}C NMR δ 49.02 (t), 52.89 (q), 75.90 (s), 102.59 (s), 127.51 (d), 128.63 (d), 131.25 (d), 137.48 (s), 139.45 (d), 150.06 (d), 185.00 (s). HRMS calcd. for $C_{14}H_{13}O_2I$ 339.996, found 339.996.



9a-Methoxy-9,9a-dihydro-fluoren-3-one (8.40)

^{1}H NMR δ 2.86 (m, 2H), 3.64 (s, 3H), 6.38 (d, *J* = 9Hz, 1H), 6.59 (s, 1H), 6.79 (d, *J* = 9 Hz, 1H), 7.05-7.08 (m, 1H), 7.28 (dt, *J* = 11 Hz, *J* = 2 Hz, 1H), 7.45-7.49 (m, 1H), 7.56-7.59 (m, 1H). ^{13}C NMR δ (42.0 (s), 49.7 (q), 83.8 (s), 121.4 (d), 125.6 (d), 126.1 (d), 127.6 (d), 127.8 (d),132.4 (d), 134.3 (s), 137.8 (s), 152.4 (d), 164.5 (s), 187.0 (s).

HRMS calc for $C_{14}H_{12}O_2$ 212.084, found 212.084. E.e. determination on HPLC DAICEL OD column, Heptane/*i*PrOH = 90/10, rt 7.2 min, 9.4 min.



N-(2,2-Dimethyl-4,4,8,8-tetraphenyl-tetrahydro[1,3]dioxolo [4,5-e][1,3,2]dioxaphosphepin-6-yl)-N,N',N'-trimethylethane -1,2-diamine (L7)

At 0°C, 2.5 mmol (1.16 g) (-) Taddol was dissolved in 10 ml of THF and 8.5 mmol Et_3N (1.25 ml) was added. To the stirred mixture slowly 2.5 mmol (236 μl) PCl_3 was added. The mixture was stirred for 1h, the salts were removed by filtration, and the chlorophoshine solution was cooled to -20°C. A premade solution of the lithiumamide of N,N',N'-trimethylethylenediamine (5 ml of THF, 3.0 mmol amine, 1.88 ml of 1.6 M *n*BuLi in hexane) was slowly added to the chlorophosphine solution, and the mixture was allowed to warm to ambient temperature, and stirred overnight.

Salts were removed by filtration, the solvents were evaporated and the product was obtained as a white powder by crystallisation from acetone (193 mg, 13%).

^{1}H NMR δ 0.28 (s, 3H), 1.29 (s, 3H), 2.23, s, 6H), 2.79 (d, *J* = 9 Hz, 3H), 4.80 (d, *J* = 9 Hz, 1H), 4.99 (dd, *J* = 9, 3 Hz, 1H), 7.18-7.82 (m, 20H). ^{13}C NMR δ 25.26, 27.51, 32.45 (d, *J* = 16 Hz), 45.56, 46.80 (d, *J* = 24 Hz), 57.87, 81.19, 82.20, 82.43, 127.14, 127.42, 127.65, 128.03, 128.73, 128.83, 128.97, 140.30 (d, *J* = 15 Hz), 145.48 (d, *J* = 15 Hz).

HRMS calcd for $C_{36}H_{41}N_2O_4P$ 596.280, found 596.281.

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